WEST

Generate Collection Print

L4: Entry 113 of 144 File: USPT Jul 9, 2002

DOCUMENT-IDENTIFIER: US 6416740 B1
TITLE: Acoustically active drug delivery systems

Brief Summary Text (9):
Another problem to be overcome in the formulation of useful delivery forms for biopolymers relates to denaturation of proteins, especially enzymes. Spray drying, particularly at elevated temperatures and/or pressures selectively denatures some proteins. Broadhead, et al., J. Pharm. Pharmocol. 1994 46:458-467, however, reports conditions of spray drying which maintain 70% yields of active .beta.-galactosidase.

Detailed Description Text (12):
"Carrier" refers to a pharmaceutically acceptable vehicle, which is a nonpolar, hydrophobic solvent, and which may serve as a reconstituting medium. The carrier may be aqueous-based or organic-based. Carriers include, inter alia, lipids, proteins, polysaccharides, sugars, polymers, copolymers, and acrylates.

Detailed Description Text (15):
"Protein" refers to molecules comprising, and preferably consisting essentially of, .alpha.-amino acids in peptide linkages. Included within the term "protein" are globular proteins such as albumins, globulins and histones, and fibrous proteins such as collagens, elastins and keratins. Also included within the term "protein" are "compound proteins," wherein a protein molecule is united with a nonprotein molecule, such as nucleoproteins, mucoproteins, lipoproteins and metalloproteins. The proteins may be naturally-occurring, synthetic or semi-synthetic.

Detailed Description Text (16):
"Stabilizing material" or "stabilizing compound" refers to any material which is capable of improving the stability of compositions containing the gases, gaseous precursors, steroid prodrugs, targeting ligands and/or other bioactive agents described herein, including, for example, mixtures, suspensions, emulsions, dispersions, vesicles, or the like. Encompassed in the definition of "stabilizing material" are certain of the present bioactive agents. The improved stability involves, for example, the maintenance of a relatively balanced condition, and may be exemplified, for example, by increased resistance of the composition against destruction, decomposition, degradation, and the like. In the case of preferred embodiments involving vesicles filled with gases, gaseous precursors, liquids, steroid prodrugs and/or bioactive agents, the stabilizing compounds may serve to either form the vesicles or stabilize the vesicles, in either way serving to minimize or substantially (including completely) prevent the escape of gases, gaseous precursors, steroid prodrugs and/or bioactive agents from the vesicles until said release is desired. The term "substantially," as used in the present context of preventing escape of gases, gaseous precursors, steroid prodrugs and/or bioactive agents from the vesicles, means greater than about 50% is maintained entrapped in the vesicles until release is desired, and preferably greater than about 60%, more preferably greater than about 70%, even more preferably greater than about 80%, still even more preferably greater than about 90%, is maintained entrapped in the vesicles until release is desired. In particularly preferred embodiments, greater than about 95% of the gases, gaseous precursors, steroid prodrugs and/or bioactive agents are maintained entrapped until release is desired. The gases, gaseous precursors, liquids, steroid prodrugs and/or bioactive agents may also be completely maintained entrapped (i.e., about 100% is maintained entrapped), until release is desired. Exemplary stabilizing materials include, for example, lipids, proteins, polymers, carbohydrates and

surfactants. The resulting mixture, suspension, emulsion or the like may comprise walls (i.e., films, membranes and the like) around the steroid prodrug, bioactive agent, gases and/or gaseous precursors, or may be substantially devoid of walls or membranes, if desired. The stabilizing may, if desired, form droplets. The stabilizing material may also comprise salts and/or sugars. In certain embodiments, the stabilizing materials may be substantially (including completely) cross-linked. The stabilizing material may be neutral, positively or negatively charged.

Detailed Description Text (17):
"Droplet" refers to a spherical or spheroidal entity which may be substantially liquid or which may comprise liquid and solid, solid and gas, liquid and gas, or liquid, solid and gas. Solid materials within a droplet may be, for example, particles, polymers, lipids, proteins, or surfactants.

Detailed Description Text (18):
"Vesicle" refers to an entity which is generally characterized by the presence of one or more walls or membranes which form one or more internal voids. Vesicles may be formulated, for example, from a stabilizing material such as a lipid, including the various lipids described herein, a proteinaceous material, including the various proteins described herein, and a polymeric material, including the various polymeric materials described herein. As discussed herein, vesicles may also be formulated from carbohydrates, surfactants, and other stabilizing materials, as desired. The lipids, proteins, polymers and/or other vesicle forming stabilizing materials may be natural, synthetic or semi-synthetic. Preferred vesicles are those which comprise walls or membranes formulated from lipids. The walls or membranes may be concentric or otherwise. The stabilizing compounds may be in the form of one or more monolayers or bilayers. In the case of more than one monolayer or bilayer, the monolayers or bilayers may be concentric. Stabilizing compounds may be used to form a unilamellar vesicle (comprised of one monolayer or bilayer), an oligolamellar vesicle (comprised of about two or about three monolayers or bilayers) or a multilamellar vesicle (comprised of more than about three monolayers or bilayers). The walls or membranes of vesicles may be substantially solid (uniform), or they may be porous or semi-porous. The vesicles described herein include such entities commonly referred to as, for example, liposomes, lipospheres, particles, nanoparticles, micelles, bubbles, microbubbles, microspheres, lipid-coated bubbles, polymer-coated bubbles and/or protein-coated bubbles, microbubbles and/or microspheres, nanospheres, microballoons, microcapsules, aerogels, clathrate bound vesicles, hexagonal H II phase structures, and the like. The internal void of the vesicles may be filled with a wide variety of materials including, for example, water, oil, gases, gaseous precursors, liquids, fluorinated liquids, liquid perfluorocarbons, liquid perfluoroethers, therapeutics, and bioactive agents, if desired, and/or other materials. The vesicles may also comprise a targeting ligand, if desired.

Detailed Description Text (22):
"Aerogel" refers to generally spherical or spheroidal entities which are characterized by a plurality of small internal voids. The aerogels may be formulated from synthetic materials (for example, a foam prepared from baking resorcinol and formaldehyde), as well as natural materials, such as carbohydrates (polysaccharides) or proteins.

Detailed Description Text (33):
"Bioactive agent" refers to a substance which may be used in connection with an application that is therapeutic or diagnostic, such as, for example, in methods for diagnosing the presence or absence of a disease in a patient and/or methods for the treatment of a disease in a patient. "Bioactive agent" also refers to substances which are capable of exerting a biological effect in vitro and/or in vivo. The bioactive agents may be neutral, positively or negatively charged. Exemplary bioactive agents include, for example, prodrugs, targeting ligands, diagnostic agents, pharmaceutical agents, drugs, synthetic organic molecules, proteins, peptides, vitamins, steroids, steroid analogs and genetic material, including nucleosides, nucleotides and polynucleotides.

Detailed Description Text (34):
"Targeting ligand" refers to any material or substance which may promote targeting of tissues and/or receptors in vivo or tit vitro with the compositions of the present invention. The targeting ligand may be synthetic, semi-synthetic, or

naturally-occurring. Materials or substances which may serve as targeting ligands include, for example, proteins, including antibodies, antibody fragments, hormones, hormone analogues, glycoproteins and lectins, peptides, polypeptides, amino acids, sugars, saccharides, including monosaccharides and polysaccharides, carbohydrates, vitamins, steroids, steroid analogs, hormones, cofactors, bioactive agents, and genetic material, including nucleosides, nucleotides, nucleotide acid constructs and polynucleotides.

Detailed Description Text (38):
"Cross-link," "cross-linked" and "cross-linking" generally refer to the linking of two or more stabilizing materials, including lipid, protein, polymer, carbohydrate, surfactant stabilizing materials and/or bioactive agents, by one ore more bridges. The bridges may be composed of one or more elements, groups, or compounds, and generally serve to join an atom from a first stabilizing material molecule to an atom of a second stabilizing material molecule. The cross-link bridges may involve covalent and/or non-covalent associations. Any of a variety of elements, groups, and/or compounds may form the bridges in the cross-links, and the stabilizing materials may be cross-linked naturally or through synthetic means. For example, cross-linking may occur in nature in material formulated from peptide chains which are joined by disulfide bonds of cystine residues, as in keratins, insulins and other proteins. Alternatively, cross-linking may be effected by suitable chemical modification, such as, for example, by combining a compound, such as a stabilizing material, and a chemical substance that may serve as a cross-linking agent, which may cause to react by, for example, exposure to heat, high-energy radiation, ultrasonic radiation and the like. Examples include cross-linking by sulfur to form disulfide linkages, cross-linking using organic peroxides, cross-linking of unsaturated materials by means of high-energy radiation, cross-linking with dimethylol carbamate, and the like. If desired, the stabilizing compounds and/or bioactive agents may be substantially cross-linked. The term "substantially" means that greater than about 50% of the stabilizing compounds contain cross-linking bridges. If desired, greater than about 60%, 70%, 80%, 90%, 95% or even 100% of the stabilizing compounds contain such cross-linking bridges. Alternatively, the stabilizing materials may be non-cross-linked, i.e., such that greater than about 50% of the stabilizing compounds are devoid of cross-linking bridges, and if desired, greater than about 60%, 70%, 80%, 90%, 95% or even 100% of the stabilizing compounds are devoid of cross-linking bridges.

Detailed Description Text (72):
Suitable proteins, or derivatives thereof, for use as surfactants in the present invention include, for example, albumin, hemoglobin, .alpha.-1-antitrypsin, .alpha.-fetoprotein, collagen, fibrin, aminotransferases, amylase, C-reactive protein, carcinoembryonic antigen, ceruloplasmin, complement, creatine phosphokinase, ferritin, fibrinogen, fibrin, transpeptidase, gastrin, serum globulins, myoglobin, immunoglobulins, lactate dehydrogenase, lipase, lipoproteins, acid phosphatase, alkaline phosphatase, .alpha.-1-serum protein fraction, .alpha.-2-serum protein fraction, .beta.-protein fraction, .gamma.-protein fraction and .gamma.-glutamyl transferase. Other proteins that may be used in the present invention are described, for example, in U.S. Pat. Nos. 4,572,203, 4,718,433, 4,774,958, and 4,957,656, the disclosures of which are hereby incorporated herein by reference in their entirety. Other protein-based surfactants, in addition to those described above and in the aforementioned patents, would be apparent to one of ordinary skill in the art, in view of the present disclosure. Polypeptides such as polyglutamic acid and polylysine may also be useful in the present invention.

Detailed Description Text (73):
In addition to surfactants formulated from lipids and/or proteins, embodiments of the present invention may also involve surfatants formulated from polymers which may be of natural, semi-synthetic (modified natural) or synthetic origin. Polymer denotes a compound comprised of two or more repeating monomeric units, and preferably 10 or more repeating monomeric units. Semi-synthetic polymer (or modified natural polymer) denotes a natural polymer that has ben chemically modified in some fashion Examples of suitable natural polymers include naturally occurring polysaccharides, such as, for example, arabinans, fructans, fucans, galactans, galacturonans, glucans, mannans, xylans (such as, for example, inulin), levan, fucoidan carrageenan, galatocarolose, pectic acid, pectins, including amylose, pullulan, glycogen, amylopectin, cellulose,

dextran, dextrin, dextrose, glucose, polyglucose, polydextrose, pustulan, chitin, agarose, keratin, chondroitin, dermatan, hyaluronic acid, alginic acid, xanthin gum, starch, such as HETA-starch, and various other natural homopolymer or heteropolymers, such as those containing one or more of the following aldoses, ketoses, acids or amines: erythrose, threose, ribose, arabinose, xylose, lyxose, allose, altrose, glucose, dextrose, mannose, gulose, idose, galactose, talose, erythrulose, ribulose, xylulose, psicose, fructose, sorbose, tagatose, mannitol, sorbitol, lactose, sucrose, trehalose, maltose, cellobiose, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, glucuronic acid, gluconic acid, glucaric acid, galacturonic acid, mannuronic acid, glucosamine, galactosamine, and neuraminic acid, and naturally occuring derivatives thereof. Accordingly, suitable polymers include, for example, proteins, such as albumin. Exemplary semi-synthetic polymers include carboxymethylcellulose, hydroxymethylcellulose, hydroxypropylmethylcellulose, methylcellulose, and methoxycellulose. Exemplary synthetic polymers suitable for use in the present invention include polyphosphazenes, polyethylenes (such as, for example, polyethylene glycol (including, for example, the class of compounds referred to as Pluronics.RTM., which are generically known as poloxamers and are commercially available from BASF, Parsippany, N.J.), polyoxyethylene, and polyethylene terephthlate), polypropylenes (such as, for example, polypropylene glycol), polyurethanes (such as, for example, polyvinyl alcohol (PVA), polyvinyl chloride and polyvinylpyrrolidone), polyamides including nylon, polystyrene, polylactic acids, fluorinated hydrocarbon polymers, fluorinated carbon polymers (such as, for example, polytetrafluoroethylene), acrylate, methacrylate, and polymethylmethacrylate, and derivatives thereof. Preferred are biocompatible synthetic polymers or copolymers prepared from monomers, such as acrylic acid, methacrylic acid, ethyleneimine, crotonic acid, acrylamide, ethyl acrylate, methyl methacrylate, 2-hydroxyethyl methacrylate (HEMA), lactic acid, glycolic acid, .epsilon.-caprolactone, acrolein, cyanoacrylate, bisphenol A, epichlorhydrin, hydroxyalkyl-acrylates, siloxane, dimethylsiloxane, ethylene oxide, ethylene glycol, hydroxyalkyl-methacrylates, N-substituted acrylamides, N-substituted methacrylamides, N-vinyl-2-pyrrolidone, 2,4-pentadiene-1-ol, vinyl acetate, acrylonitrile, styrene, p-amino-styrene, p-amino-benzyl-styrene, sodium styrene sulfonate, sodium 2-sulfoxyethyl-methacrylate, vinyl pyridine, aminoethyl methacrylates, 2-methacryloyloxy-trimethylammonium chloride, and polyvinylidene, as well polyfunctional crosslinking monomers such as N,N'-methylenebisacrylamide, ethylene glycol dimethacrylates, 2,2'-(p-phenylenedioxy)-diethyl dimethacrylate, divinylbenzene, triallylamine, polylactidecoglycolide, polyethylene-polypropyleneglycol, and methylenebis-(4-phenylisocyanate), including combinations thereof. Preferable polymers include polyacrylic acid, polyetyleneimine, polymethacrylic acid, polymethylmethacrylate, polysiloxane, polydimethylsiloxane, polylactic acid, poly(.epsilon.-caprolactone), epoxy resin, poly(ethylene oxide), poly(ethylene glycol), and polyamide (nylon) polymers. Preferable copolymers include the following: polyvinylidene-polyacrylonitrile, polyvinylidene-polyacrylonitrile-polymethylmethacrylate, polystyrene-polyacrylonitrile and poly d-1, lactide co-glycolide polymers. A preferred copolymer is polyvinylidene-polyacrylonitrile. Other suitable biocompatible monomers and polymers will be apparent to those skilled in the art, in view of the present disclosure.

Detailed Description Text (79):
The introduction of fluorine into the surfactant may also be accomplished by forming microspheres in the presence of a perfluorocarbon gas. For example, when microspheres are formed from proteins such as human serum albumin in the presence of a perfluorocarbon gas, such as perfluoropropane, using mechanical cavitation, fluorine from the gas phase becomes bound to the protein shell during formation. The presence of fluorine in the shell material can be later detected by NMR of shell debris which has been purified from disrupted microspheres. Fluorine can also be introduced into microsphere shell material using other methods for forming microspheres, such as sonication, spray-drying or emulsification techniques.

Detailed Description Text (80):
Another way in which fluorine can be introduced is by using a fluorine-containing reactive compound. The term "reactive compound" refers to compounds which are capable of interacting with the surfactant in such a manner that fluorine moieties become covalently attached to thereto. When the surfactant is a protein, preferred reactive compounds are either alkyl esters or acyl halides which are capable of reacting with

the protein's amino groups to form an amide linkage via an acylation reaction (see ADVANCED ORGANIC CHEMISTRY pp. 417-418 (John Wiley & Sons, New York, N.Y., 4th ed., 1992) the disclosures of which are hereby incorporated herein by reference in their entirety). The reactive compound can be introduced at any stage during microsphere formation, but is preferably added to the gas phase prior to microsphere formation. For example, when microspheres are to be made using mechanical or ultrasound cavitation techniques, the reactive compound can be added to the gas phase by bubbling the gas to be used in the formation of the microspheres (starting gas) through a solution of the reactive compound. This solution is kept at a constant temperature which is sufficient to introduce a desired amount of reactive compound into the gas phase. The resultant gas mixture, which now contains the starting gas and the reactive compound, is then used to form microspheres. The microspheres are preferably formed by sonication of human serum albumin in the presence of the gas mixture as described in U.S. Pat. No. 4,957,656, the disclosures of which are hereby incorporated herein by reference in their entirety.

Detailed Description Text (84):
It is not always possible to determine whether a given material is a basic or an auxiliary agent, since the functioning of the material is determined empirically, for example, by the results produced with respect to producing surfactants. As an example of how the basic and auxiliary materials may function, it has been observed that the simple combination of a biocompatible lipid and water or saline when shaken will often give a cloudy solution subsequent to autoclaving for sterilization. Such a cloudy solution may function as a contrast agent, but is aesthetically objectionable and may imply instability in the form of undissolved or undispersed lipid particles. Cloudy solutions may also be undesirable where the undissolved particulate matter has a diameter of greater than about 7 .mu.m, and especially greater than about 10 .mu.m. Manufacturing steps, such as sterile filtration, may also be problematic with solutions which contain undissolved particulate matter. Thus, propylene glycol may be added to remove this cloudiness by facilitating dispersion or dissolution of the lipid particles. Propylene glycol may also function as a wetting agent which can improve vesicle formation and stabilization by increasing the surface tension on the vesicle membrane or skin. It is possible that propylene glycol can also function as an additional layer that may coat the membrane or skin of the vesicle, thus providing additional stabilization. Compounds used to make mixed micelle systems also may be used as basic or auxiliary stabilizing materials. Clathrates may also be useful in the preparation of surfactants for use in the present invention, see for example WO 90/01952, the disclosure of which is incorporated herein by reference in its entirety.

Detailed Description Text (87):
The stability of vesicles may be attributable, at least in part, to the materials from which the vesicles are made, including, for example, the lipids, polymers, proteins and/or surfactants described above, and it is often not necessary to employ additional stabilizing materials, although it is optional and may be preferred to do so. In addition to, or instead of, the lipid, protein and/or polymer compounds discussed above, the compositions described herein may comprise one or more other stabilizing materials. Exemplary stabilizing materials include, for example, surfactants and biocompatible polymers. The stabilizing materials may be employed to desirably assist in the formation of vesicles and/or to assure substantial encapsulation of the gases, gaseous precursors and/or therapeutic. Even for relatively insoluble, non-diffusible gases, such as perfluoropropane or sulfur hexafluoride, improved vesicle compositions may be obtained when one or more stabilizing materials are utilized in the formation of the gas and/or gaseous precursor filled vesicles. These compounds may help improve the stability and the integrity of the vesicles with regard to their size, shape and/or other attributes.

Detailed Description Text (88):
Like the polymers discussed above, the biocompatible polymers useful as stabilizing materials for preparing the gas and/or gaseous precursor filled vesicles may be of natural, semi-synthetic (modified natural) or synthetic origin. Exemplary natural polymers include naturally occurring polysaccharides, such as, for example, arabinans, fructans, fucans, galactans, galacturonans, glucans, mannans, xylans (such as, for example, inulin), levan, fucoidan, carrageenan, galatocarolose, pectic acid, pectins, including amylose, pullulan, glycogen, amylopectin, cellulose, dextran, dextrin,

dextrose, glucose, polyglucose, polydextrose, pustulan, chitin, agarose, keratin, chondroitin, dermatan, hyaluronic acid, alginic acid, xanthan gum, starch and various other natural homopolymer or heteropolymers, such as those containing one or more of the following aldoses, ketoses, acids or amines: erythrose, threose, ribose, arabinose, xylose, lyxose, allose, altrose, glucose, dextrose, mannose, gulose, idose, galactose, talose, erythrulose, ribulose, xylulose, psicose, fructose, sorbose, tagatose, mannitol, sorbitol, lactose, sucrose, trehalose, maltose, cellobiose, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, glucuronic acid, gluconic acid, glucaric acid, galacturonic acid, mannuronic acid, glucosamine, galactosamine, and neuraminic acid, and naturally occurring derivatives thereof. Accordingly, suitable polymers include, for example, proteins, such as albumin. Exemplary semi-synthetic polymers include carboxymethylcellulose, hydroxymethylcellulose, hydroxypropylmethylcellulose, methylcellulose, and methoxycellulose. Exemplary synthetic polymers include polyphosphazenes, polyethylenes (such as, for example, polyethylene glycol (including the class of compounds referred to as Pluronics.RTM., commercially available from BASF, Parsippany, N.J.), polyoxyethylene, and polyethylene terephthlate), polypropylenes (such as, for example, polypropylene glycol), polyurethanes (such as, for example, polyvinyl alcohol (PVA), polyvinyl chloride and polyvinylpyrrolidone), polyamides including nylon, polystyrene, polylactic acids, fluorinated hydrocarbon polymers, fluorinated carbon polymers (such as, for example, polytetrafluoroethylene), acrylate, methacrylate, and polymethylmethacrylate, and derivatives thereof. Methods for the preparation of vesicles which employ polymers as stabilizing compounds will be readily apparent to those skilled in the art, in view of the present disclosure, when coupled with information known in the art, such as that described and referred to in Unger, U.S. Pat. No. 5,205,290, the disclosure of which is hereby incorporated herein by reference in its entirety.

Detailed Description Text (116):
The introduction of fluorine into stabilizing materials and/or vesicles may also be accomplished by forming vesicles in the presence of a perfluorocarbon gas. For example, when vesicles are formed from proteins, such as human serum albumin in the presence of a perfluorocarbon gas, such as perfluoropropane, using mechanical cavitation, fluorine from the gas phase becomes bound to the protein vesicles during formation. The presence of fluorine in the vesicles and/or stabilizing materials can be detected by NMR of vesicle debris which has been purified from disrupted vesicles. Fluorine can also be introduced into stabilizing materials and/or vesicles using other methods, such as sonication, spray-drying or emulsification techniques. Another way in which fluorine can be introduced into the shell material is by using a fluorine-containing reactive compound. The term "reactive compound" refers to compounds which are capable of interacting with the stabilizing material and/or vesicle in such a manner that fluorine moieties become covalently attached to the stabilizing material and/or vesicle. When the stabilizing material is a protein, preferred reactive compounds are either alkyl esters or acyl halides which are capable of reacting with the protein's amino groups to form an amide linkage via an acylation reaction. The reactive compound can be introduced at any stage during vesicle formation, but is preferably added to the gas phase prior to vesicle formation. For example, when vesicles are to be made using mechanical or ultrasound cavitation techniques, the reactive compound can be added to the gas phase by bubbling the gas to be used in the formation of the vesicles (starting gas) through a solution of the reactive compound into the gas phase. The resultant gas mixture, which now contains the starting gas and the reactive compound, is then used to form vesicles. The vesicles are preferably formed by sonication of human serum albumin in the presence of a gas mixture, as described in U.S. Pat. No. 4,957,656, the disclosure of which is hereby incorporated herein by reference in its entirety.

Detailed Description Text (125):
Other suitable therapeutics include, antifungal agents, and bioactive agents, such as for example, antineoplastic agents, such as platinum compounds (e.g., spiroplatin, cisplatin, and carboplatin), methotrexate, adriamycin, taxol, mitomycin, ansamitocin, bleomycin, cytosine arabinoside, arabinosyl adenine, mercaptopolylysine, vincristine, busulfan, chlorambucil, melphalan (e.g., L-sarolysin (L-PAM, also known as Alkeran) and phenylalanine mustard (PAM)), mercaptopurine, mitotane, procarbazine hydrochloride, dactinomycin (actinomycin D), daunorubicin hydrochloride, doxorubicin hydrochloride, mitomycin, plicamycin (mithramycin), aminoglutethimide, estramustine

phosphate sodium, flutamide, leuprolide acetate, megestrol acetate, tamoxifen citrate, testolactone, trilostane, amsacrine (m-AMSA), asparaginase (L-asparaginase) Erwina asparaginase, etoposide (VP-16), interferon .alpha.-2a, interferon .alpha.-2b, teniposide (VM-26), vinblastine sulfate (VLB), vincristine sulfate, bleomycin, bleomycin sulfate, methotrexate, adriamycin, carzelesin, and arabinosyl; blood products such as parenteral iron, hemin, hematoporphyrins and their derivatives; biological response modifiers such as muramyldipeptide, muramyltripeptide, prostaglandins, microbial cell wall components, lymphokines (e.g., bacterial endotoxin such as lipopoly-saccharide, macrophage activation factor), sub-units of bacteria (such as Mycobacteria and Corynebacteria), the synthetic dipeptide N-acetyl-muramyl-L-alanyl-D-isoglutamine; anti-fungal agents such as ketoconazole, nystatin, griseofulvin, flucytosine (5-fc), miconazole, amphotericin B, ricin, and .beta.-lactam antibiotics (e.g., sulfazecin); hormones such as growth hormone, melanocyte stimulating hormone, estradiol, beclomethasone dipropionate, betamethasone, betamethasone acetate and betamethasone sodium phosphate, vetamethasone disodium phosphate, vetamethasone sodium phosphate, cortisone acetate, dexamethasone, dexamethasone acetate, dexamethasone sodium phosphate, flunsolide, hydrocortisone, hydrocortisone acetate, hydrocortisone cypionate, hydrocortisone sodium phosphate, hydrocortisone sodium succinate, methylprednisolone, methylprednisolone acetate, methylprednisolone sodium succinate, paramethasone acetate, prednisolone, prednisolone acetate, prednisolone sodium phosphate, prednisolone tebutate, prednisone, triamcinolone, triamcinolone acetonide, triamcinolone diacetate, triamcinolone hexacetonide, fludrocortisone. acetate, progesterone, testosterone, and adrenocorticotropic hormone; vitamins such as cyanocobalamin neinoic acid, retinoids and derivatives such as retinol palmitate, .alpha.-tocopherol, naphthoquinone, cholecalciferol, folic acid, and tetrahydrofolate; peptides, such as angiostatin, manganese super oxide dismutase, tissue plasminogen activator, glutathione, insulin, dopamine, peptides with affinity for the GPIIbIIIa receptor (usually found on activated receptor platelets) such as RGD, AGD, RGE, KGD, KGE, and KQAGDV, opiate peptides (such as enkephalines and endorphins), human chorionic gonadotropin, corticotropin release factor, cholecystokinins, bradykinins, promoters of bradykinins, inhibitors of bradykinins, elastins, vasopressins, pepsins, glucagon, substance P (a pain moderation peptide), integrins, Angiotensin Converting Enzyme (ACE) inhibitors (such as captopril, enalapril, and lisinopril), adrenocorticotropic hormone, oxytocin, calcitonins, IgG, IgA, IgM, ligands for Effector Cell Protease Receptors, thrombin, streptokinase, urokinase, Protein Kinase C, interferons (such as interferon .alpha., interferon .beta., and interferon .gamma.), colony stimulating factors, granulocyte colony stimulating factors, granulocyte-macrophage colony stimulating factors, tumor necrosis factors, nerve growth factors, platelet derived growth factors, lymphotoxin, epidermal growth factors, fibroblast growth factors, vascular endothelial cell growth factors, erythropoeitin, transforming growth factors, oncostatin M, interleukins (such as interleukin 1, interleukin 2, interleukin 3, interleukin 4, interleukin 5, interleukin 6, interleukin 7, interleukin 8, interleukin 9, interleukin 10, interleukin 11, and interleukin 12.), metalloprotein kinase ligands, and collagenases; enzymes such as alkaline phosphatase and cyclooxygenases; anti-allergic agents such as amelexanox; anti-coagulation agents such as phenprocoumon and heparin; circulatory drugs such as propranolol; metabolic potentiators such as glutathione; antituberculars such as para-aminosalicylic acid, isoniazid, capreomycin sulfate cycloserine, ethambutol hydrochloride ethionanide, pyrazinamide, rifampin, and streptomycin sulfate; antivirals such as acyclovir, amantadine azidothymidine (AZT or Zidovudine), ribavirin, amantadine, vidarabine, and vidarabine monohydrate (adenine arabinoside, ara-A); antianginals such as diltiazem, nifedipine, verapamil, erythrityl tetranitrate, isosorbide dinitrate, nitroglycerin (glyceryl trinitrate) and pentaerythritol tetranitrate; anticoagulants such as phenprocoumon, heparin; antibiotics such as dapsone, chloramphenicol, neomycin, cefaclor, cefadroxil, cephalexin, cephradine erythromycin, clindamycin, lincomycin, amoxicillin, ampicillin, bacampicillin, carbenicillin, dicloxacillin, cyclacillin, picloxacillin, hetacillin, methicillin, nafcillin, oxacillin, penicillin G, penicillin V, ticarcillin, rifampin and tetracycline; antiinflammatories such as difimisal, ibuprofen, indomethacin, meclofenamate, mefenamic acid, naproxen, oxyphenbutazone, phenylbutazone, piroxicam, sulindac, tolmetin, aspirin and salicylates; antiprotozoans such as chloroquine, hydroxychloroquine, metronidazole, quinine and meglumine antimonate; antirheumatics such as penicillamine; narcotics such as paregoric and opiates such as codeine, heroin, methadone, morphine and opium; cardiac glycosides such as deslanoside, digitoxin, digoxin, digitalin and digitalis; neuromuscular blockers such as atracurium

besylate, gallamine triethiodide, hexafluorenium bromide, metocurine iodide, pancuronium bromide, succinylcholine chloride (suxamethonium chloride), tubocurarine chloride and vecuronium bromide; sedatives (hypnotics) such as amobarbital, amobarbital sodium, aprobarbital, butabarbital sodium, chloral hydrate, ethchlorvynol, ethinamate, flurazepam hydrochloride, glutethimide, methotrimeprazine hydrochloride, methyprylon, midazolam hydrochloride, paraldehyde, pentobarbital, pentobarbital sodium, phenobarbital sodium, secobarbital sodium, talbutal, temazepam and triazolam; local anesthetics such as bupivacaine hydrochloride, chloroprocaine hydrochloride, etidocaine hydrochloride, lidocaine hydrochloride, mepivacaine hydrochloride, procaine hydrochloride and tetracaine hydrochloride; general anesthetics such as droperidol, etomidate, fentanyl citrate with droperidol, ketamine hydrochloride, methohexital sodium and thiopental sodium; and radioactive particles or ions such as strontium, iodide rhenium, technetium, cobalt, and yttrium. In certain preferred embodiments, the bioactive agent is a monoclonal antibody, such as a monoclonal antibody capable of binding to melanoma antigen.

Detailed Description Text (126):
Certain preferred therapeutics, such as for the treatment of ophthalmologic diseases and prostate cancer, for example, include ganciclovir, vascular endothelial growth factor, foscarnet, S-(1,3 hydroxyl-2-phosphonylmethoxypropyl) cytosine, nitric oxide synthase inhibitors, aldose reductase inhibitors (such as sorbinil and tolrestat), LY333531 (an isozyme-selective inhibitor of protein kinase C-.beta., see Faul, et al., "Synthesis of LY333531, an isozyme selective inhibitor of protein kinase C-.beta.", Abstracts of papers of the American Chemical Society 1997 213, part 2, 567, the disclosure of which is incorporated herein by reference in its entirety), cidofovir, vitamin E, aurintricarboxylic acid, somatuline, Trolox.TM., sorvudine, .alpha.-interferon, etofibrate, filgastrim, aminoguanidine, ticlopidine, ponalrestat, epalrestat, granulocyte macrophage colony stimulating factor (GM-CSF), dipyridamole+aspirin, nipradilol, haloperidol, latanoprost, dipifevrin, vascular endothelial growth factor, timolol, dorzolamide, adaprolol enantiomers, bifemelane hydrochloride, apraclonidine hydrochloride, vaninolol, betaxolol, etoposide, 3-.alpha., 5-.beta.-tetrahydrocortisol, pilocarpine, bioerodible poly(ortho ester), levobunolol, prostanoic acid, N-4 sulphanol benzyl-imidazole, imidazo pyridine, 3-(Bicyclyl methylene) oxindole, 15-deoxy spergualin, benzoylcarbinol salts, fumagillin, lecosim, bendazac, N-acyl-5-hydroxytryptamine, cetrorelix acetate, 17-.alpha.-acyl steroids, azaandrosterone, 5-.alpha.-reductase inhibitor, and antiestrogenics (such as 2-4-{1,2-diphenyl-1-butenyl}phenoxy)-N,N-dimethylethanamine).

Detailed Description Text (127):
Other preferred therapeutics include genetic material such as nucleic acids, RNA, and DNA, of either natural or synthetic origin, including recombinant RNA and DNA and antisense RNA and DNA. Types of genetic material that may be used include, for example, genes carried on expression vectors such as plasmids, phagemids, cosmids, yeast artificial chromosomes (YACs), and defective or "helper" viruses, antigene nucleic acids, both single and double stranded RNA and DNA and analogs thereof, such as phosphorothioate and phosphorodithioate oligodeoxynucleotides. Additionally, the genetic material may be combined, for example, with proteins or other polymers. Examples of genetic material that may be applied using the liposomes of the present invention include, for example, DNA encoding at least a portion of LFA-3, DNA encoding at least a portion of an HLA gene, DNA encoding at least a portion of dystrophin, DNA encoding at least a portion of CFTR, DNA encoding at least a portion of IL-2, DNA encoding at least a portion of TNF, and an antisense oligonucleotide capable of binding the DNA encoding at least a portion of Ras.

Detailed Description Text (128):
DNA encoding certain proteins may be used in the treatment of many different types of diseases. For example, adenosine deaminase may be provided to treat ADA deficiency; tumor necrosis factor and/or interleukin-2 may be provided to treat advanced cancers; HDL receptor may be provided to treat liver disease; thymidine kinase may be provided to treat ovarian cancer, brain tumors, or HIV infection; HLA-B7 may be provided to treat malignant melanoma; interleukin-2 may be provided to treat neuroblastoma, malignant melanoma, or kidney cancer; interleukin-4 may be provided to treat cancer; HIV env may be provided to treat HIV infection; antisense ras/p53 may be provided to treat lung cancer; and Factor VIII may be provided to treat Hemophilia B. See, for

example, Science 258:744-746.

Detailed Description Text (129):
Dyes are included within the definition of therapeutics. Dyes may be useful for identifying the location of a vesicle within a patient's body or particular region of a patient's body. Following administration of the vesicle compositions, and locating, with energy, such compositions within a region of a patient's body to be treated, the dye may be released from the composition and visualized by energy. Dyes useful in the present invention include fluorescent dyes and colorimetric dyes, such as sudan black, fluorescein, R-Phycoerythrin, texas red, BODIPY FL, oregon green, rhodamine red-X, tetramethylrhodamine, BODIPY TMR, BODIPY-TR, YOYO-1, DAPI, Indo-1, Cascade blue, fura-2, amino methylcoumarin, FM1-43, NBD, carbosy-SNARF, lucifer yellow, dansyl+R--NH.sub.2, propidium iodide, methylene blue, bromocresol blue, acridine orange, bromophenol blue, 7-amino-actinomycin D, allophycocyanin, 9-azidoacridine, benzoxanthene-yellow, bisbenzidide H 33258 fluorochrome, 3HCl, 5-carboxyfluorescein diacetate, 4-chloro-1-naphthol, chromomycin-A.sub.3, DTAF, DTNB, ethidium bromide, fluorescein-5-maleimide diacetate, mithramycin A, rhodamine 123, SBFI, SIST, tetramethylbenzidine, tetramethyl purpurate, thiazolyl blue, TRITC, and the like. Fluorescein may be fluorescein isothiocyanate. The fluorescein isothiocyanate, includes, inter alia, fluorescein isothiocyanate albumin, fluorescein isothiocyanate antibody conjugates, fluorescein isothiocyanate .alpha.-bungarotoxin, fluorescein isothiocyanate- casein, fluorescein isothiocyanate-dextrans, fluorescein isothiocyanate--insulin, fluorescein isothiocyanate--Lectins, fluorescein isothiocyanate--peroxidase, and fluorescein isothiocyanate--protein A.

Detailed Description Text (169):
The compositions of the present invention may be prepared using any of a variety of suitable methods. These are described below separately for the embodiments involving a targeted therapeutic delivery system comprising an oil, a surfactant, a therapeutic, and a gas, including a gas filled vesicle, and a targeted therapeutic delivery system comprising an oil, a surfactant, a therapeutic, and a gaseous precursor including a gaseous precursor filled vesicle. A targeting ligand may be attached to the surfactant of the targeted therapeutic delivery system by bonding to one or more of the materials employed in the compositions from which they are made, including the steroid prodrugs, lipids, proteins, polymers, and/or auxiliary stabilizing materials.

Detailed Description Text (251):
Vesicle compositions which comprise vesicles formulated from proteins, such as albumin vesicles, may be prepared by various processes, as will be readily apparent to those skilled in the art in view of the present disclosure. Suitable methods include those described, for example, in U.S. Pat. Nos. 4,572,203, 4,718,433, 4,774,958, and 4,957,656, the disclosures of each of which are hereby incorporated herein by reference in their entirety. Included among the methods are those which involve sonicating a solution of a protein. In preferred form, the starting material may be an aqueous solution of a heat-denaturable, water-soluble biocompatible protein. The encapsulating protein is preferably heat-sensitive so that it can be partially insolubilized by heating during sonication. Suitable heat-sensitive proteins include, for example, albumin, hemoglobin, and collagen, preferably, the protein is a human protein, with human serum albumin (HSA) being more preferred. HSA is available commercially as a sterile 5% aqueous solution, which is suitable for use in the preparation of protein- based vesicles. As would be apparent to one of ordinary skill in the art, other concentrations of albumin, as well as other proteins which are heat-denaturable, can be used to prepare the vesicles. Generally speaking, the concentration of HSA can vary and may range from about 0.1 to about 25% by weight, and all combinations and subcombinations of ranges therein. It may be preferable, in connection with certain methods for the preparation of protein-based vesicles, to utilize the protein in the form of a dilute aqueous solution. For albumin, it may be preferred to utilize an aqueous solution containing from about 0.5 to about 7.5% by weight albumin, with concentrations of less than about 5% by weight being preferred, for example, from about 0.5 to about 3% by weight.

Detailed Description Text (252):
Protein-based vesicles may be prepared using equipment which is commercially available. For example, in connection with a feed preparation operation as disclosed, for example, in U.S. Pat. No. 4,957,656, stainless steel tanks which are commercially

available from Walker Stainless Equipment Co. (New Lisbon, Wis.), and process filters which are commercially available from Millipore (Bedford, Mass.), may be utilized.

Detailed Description Text (255):
Suitable methods for the preparation of protein-based vesicles may also involve physically or chemically altering the protein or protein derivative in aqueous solution to denature or fix the material. For example, protein-based vesicles may be prepared from a 5% aqueous solution of HSA by heating after formation or during formation of the contrast agent via sonication. Chemical alteration may involve chemically denaturing or fixing by binding the protein with a difunctional aldehyde, such as gluteraldehyde. For example, the vesicles may be reacted with 0.25 grams of 50% aqueous gluteraldehyde per gram of protein at pH 4.5 for 6 hours. The unreacted gluteraldehyde may then be washed away from the protein.

Detailed Description Text (256):
In any of the techniques described above for the preparation of protein-based stabilizing materials and/or vesicles, the steroid prodrugs and/or targeting ligands may be incorporated with the proteins before, during or after formation of the vesicles, as would be apparent to one of ordinary skill in the art, based on the present disclosure. Vesicle compositions which comprise vesicles formulated from polymers may be prepared by various processes, as will be readily apparent to those skilled in the art in view of the present disclosure. Exemplary processes include, for example, interfacial polymerization, phase separation and coacervation, multiorifice centrifugal preparation, and solvent evaporation. Suitable procedures which may be employed or modified in accordance with the present disclosure to prepare vesicles from polymers include those procedures disclosed in U.S. Pat. Nos. 4,179,546, 3,945,956, 4,108,806, 3,293,114, 3,401,475, 3,479,811, 3,488,714, 3,615,972, 4,549,892, 4,540,629, 4,421,562, 4,420,442, 4,898,734, 4,822,534, 3,732,172, 3,594,326, and 3,015,128; Japan Kokai Tokkyo Koho 62 286534, British Patent No. 1,044,680, Deasy, Microencapsulation and Related Drug Processes, Vol. 20, Chs. 9 and 10, pp. 195-240 (Marcel Dekker, Inc., N.Y., 1984), Chang et al., Canadian J. of Physiology. and Pharmacology, 44:115-129 (1966), and Chang, Science, 146:524-525 (1964), the disclosures of each of which are hereby incorporated herein by reference in their entirety.

Detailed Description Text (291):
The steroid prodrugs formulated with penetration enhancing agents, known to those skilled in the art and described above, may be administered transdermally in a patch or reservoir with a permeable membrane applied to the skin. The use of rupturing ultrasound may increase transdermal delivery of therapeutic compounds, including the steroid prodrugs of the present invention. Further, an imaging mechanism may be used to monitor and modulate delivery of the steroid prodrugs. For example, diagnostic ultrasound may be used to visually monitor the bursting of the gas filled vesicles and modulate drug delivery and/or a hydrophone may be used to detect the sound of the bursting of the gas filled vesicles and modulate drug delivery.

Detailed Description Text (297):
Drug release and/or vesicle rupture can be monitored ultrasonically by several different mechanisms. Bubble or vesicle destruction results in the eventual dissolution of the ultrasound signal. However, prior to signal dissolution, the delivery vehicles/vesicles provide an initial burst of signal. In other words, as increasing levels of ultrasound energy are applied to the treatment zone containing the delivery vehicles/vesicles, there is a transient increase in signal. This transient increase in signal may be recorded at the fundamental frequency, the harmonic, odd harmonic or ultraharmonic frequency.

Other Reference Publication (8):
Faul et al., "Synthesis of LY333531, an isozyme selective inhibitor of protein kinase C-.beta.", Abstrs. of papers of the American Chem. Soc., Part 2, 1997, 213th ACS National Meeting, 567.

Other Reference Publication (128):
Brown et al., "Transdermal Delivery of Drugs", Ann. Rev. Med., 1988, 39, 221-229.

WEST Search History

DATE: Thursday, May 15, 2003

Set Name side by side	Query	Hit Count	Set Name result set
	DB=USPT,PGPB,JPAB,EPAB,DWPI,TDBD; PLUR=YES; OP=OR		
L26	L25 and hydrophobic adj3 drug	90	L26
L25	L24 and transdermal	3104	L25
L24	matrix and polymers and surfactant	22862	L24
L23	L22 and hydrophobic adj6 drug	30	L23
L22	transdermal and (two or second) adj3 polymers and surfactant	171	L22
L21	transdermal and (two or second) adj3 polymers and sufactant	1	L21
L20	transdermal (two or second) adj3 polymers and sufactant	26110	L20
L19	transdermal and matrix and (two or second) adj3 polymers and hydrophobic adj2 drug and surfactant	20	L19
L18	transdermal and matrix and (two or second) adj3 polymers and hydrophobic adj2 drug	23	L18
L17	L16 and matrix	40	L17
L16	patch and hydrophobic adj3 drug and surfactant and transdermal	54	L16
L15	estrogen and patch and hydrophobic adj3 drug and surfactant and transdermal	11	L15
L14	estrogen adj5 patch and hydrophobic adj3 drug and surfactant	0	L14
L13	estrogen adj3 patch and hydrophobic adj3 drug and surfactant	0	L13
L12	L11 and oleic	20	L12
L11	transdermal and surfactant and hydrophobic adj3 drug and patch	54	L11
L10	transdermal and surfactant and hydrophobic adj3 drug and oleic and penetration adj3 enhancer	3	L10
L9	transdermal and surfactant and hydrophobic adj3 drug and oleic	35	L9
L8	transdermal adj5 surfactant and hydrophobic adj3 drug and oleic	0	L8
L7	transdermal same surfactant and hydrophobic adj3 drug and oleic	2	L7
L6	L5 and transdermal	4	L6
L5	protein adj3 based adj3 surfactants	67	L5
L4	L3 and transdermal	144	L4
L3	L2 and dissolution	764	L3
L2	L1 and protein	3518	L2
L1	albumin same surfactant	3860	L1

END OF SEARCH HISTORY

WEST Search History

DATE: Thursday, May 15, 2003

Set Name side by side	**Query**	**Hit Count**	**Set Name** result set
DB=USPT,PGPB,JPAB,EPAB,DWPI,TDBD; PLUR=YES; OP=OR			
L3	L2 and substrate	559	L3
L2	L1 and carrier	918	L2
L1	estrogen and transdermal and surfactant	969	L1

END OF SEARCH HISTORY